Review Article

Clinical trials in nutrition

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Trials of nutritional intervention in a wide range of health and disease states, preventive and therapeutic, are required. Not only has the emergence of chronic non-communicable disease (CNCD) with acknowledged nutritional pathogenesis created this imperative need, but so also have other conditions which, previously, had not been regarded as nutritionally based. Among the latter are health problems associated with ageing: the menopause, a decline in immune function, and a decline in cognitive function. At the same time, there is a new set of materno-foetal and infant nutrition issues for investigation which relate to new food exposures and the long-term effects of nutritionally mediated gene expression. The emergence of the new food science of phytochemicals with human biological importance also sets the scene for their evaluation in traditional diets and novel foods. Such trials are more complex than comparable pharmacotherapeutic studies because of the complexity of food chemistry, as well as the food behavioural changes which may accompany a nutritional intervention, and the general problem of there not being a 'gold standard' for food intake methodology. Choice of study population is also a key issue in relation to the extrapolation of findings from a particular trial, with population representativeness being an advantage. In order to obtain useful information on manageable sample sizes, either intermediate end-points (short of morbidity and mortality) need to be studied or high-risk groups (such as the aged) need to be recruited. There are some unique ethical issues which must inform clinical nutrition trials. These include certain preventive imperatives like the right to be fed, the risks in disruption of food cultures and the need for food security and sustainability. Rapid changes in the food supply do, however, make such trials more important, while the value of food-health knowledge that cannot be obtained by trial must still be appreciated.

Key words: nutrition intervention, nutritional epidemiology, food trial, nutrition trial, compliance.

The rationale for nutritional clinical trials

Why trials in food and nutrition?

The observational and interventional stimulus of nutritional epidemiology. For most of human history, changes in the way we eat and the associated health changes have been slow, with efforts to improve health through food being made by trial and error.[1] The changes, for example, on migration or with major environmental change, may have been accepted or not appreciated. For example, the development of iodine deficiency disorders in a region may have been regarded as 'the way things are' or not attributed to food, although it is possible that importation of iodine-containing food items, with the resultant improvement of the problem, or migration to another area, with a decrease in prevalence, raised the possibility that a food factor might have been responsible.[2]

In more recent times, the formalization of such observations by way of nutritional epidemiology and clinical epidemiology has created opportunities for testing food and applying food factor solutions to the problems.[3] Such evaluation may proceed by way of a community-based intervention; for example, by introducing iodized salt or a seaweed- or seafood-based product and measuring the change in prevalence. There have been numerous such trials, many of which have resulted in specific micronutrient deficiencies being considered major factors in the prevalence of disease. These would include feeding programs for protein–energy malnutrition (PEM);[4] iron supplementation or food fortification with iron for impaired cognitive function; or in microcytic hypochromic anaemia with increased iron intake; or a vitamin A supplementation or food fortification to prevent xerophthalmia.[5–8]

Definition and acceptability of risk. Intervention trials, especially with micronutrients, have raised the prospect of demonstrating major benefits for a large fraction of the population and, although risk has generally been considered, it has not necessarily been defined and has been far outweighed by potential benefits. The lower the prevalence of the health problem, the less acceptable is the risk of a food or food vehicle intervention and the greater the need for risk definition.[9] Thus, there has been considerable controversy about the introduction of food fortification with folate, which would affect consumption community-wide, in an effort to reduce the incidence of neural tube defects when a more targetted

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approach using folate supplementation for women whose offspring are at risk might do just as well.[10,11] Traditional food cultures and health problems may provide clues as to appropriate risk–benefit studies. For example, Chinese women traditionally use one of the best food sources of folate, namely chicken liver, throughout their reproductive years and then reduce their intake at a time when they are developing atrophic gastritis and a reduced capacity to absorb vitamin B-12, a deficiency in which may be exacerbated by folate.

Clinical trials which understand and characterize at-risk groups and offer them potential benefits through the use of particular foods or food components will be of increasing interest as the era of an inadequate food supply and related deficiency disorders recedes, and as the economic and educational status of populations improves. Such populations will be able to afford, and will want to be selective about, the food they choose in relation to their health.

The recognition of the relationships between food intakes and major non-communicable diseases (NCD) (e.g. cardiovascular, neoplastic and osteoporotic diseases, obesity, diabetes) initially stimulated the development of dietary guidelines for the public at large,[12] and now encourages a more selective approach based on a knowledge of genetic predisposition and of related lifestyle factors (e.g. physical activity, tobacco and alcohol consumptions, other substance abuse), and the health care system in which the individual operates.[13] Again clinical trials will come to the fore in establishing the relationship between food intakes and NCD.

Consequences of major changes in food intake. The lessons so far for NCD are that in some health domains major improvements appear to have been made with regard to nutritional advice and change (e.g. reduce ischaemic heart disease through lowered saturated fat intake and possibly through increased polyunsaturated fat intake);[14] however, the full health consequences of major changes in food intake tend not to be evaluated. For example, the change in fat quality towards ω-6 fatty acids and away from saturated fat, which began at the end of the 1960s, has scarcely been evaluated beyond hyperlipidaemia.[15] Indeed, it is only now, 30 years or so later, that questions are being systematically asked about the safe upper limit of ω-6 fatty acid consumption.[16,17] In future, it will be necessary to approach such novel changes to the human diet, such as those regarding fat amounts and quality, with clinical trials and with the appropriate toxicology (as best we know it at the time).

For other NCD, surprisingly little change has taken place in prevalence or incidence despite an apparently good appreciation of dietary linkages. Colorectal cancer (CRC) is an example, although[18–21] the problem may in part be the competing effects of factors which increase and those which decrease risk. For example, if (saturated) fat increases the risk of CRC[22,23] and whey proteins in milk decrease the risk,[24] reduced dairy product consumption may not benefit those at risk of this cancer. Or, without the present nutritional changes in fat, fruit, vegetable and cereal intake, the incidence of CRC may have been even higher. Randomized clinical trials over long time frames may be needed to resolve these issues. The problem will be the cost and management of such research exercises as these may be so prohibitive that other methods of enquiry may be required. Alternatively the approach may not be ethically implementable for the outcome in question.[25]

Development of criteria. Any clinical trial should satisfy at least three basic criteria before initiation: (i) plausibility of hypothesis; (ii) feasibility; and (iii) justifiable cost (of the study and of the envisaged nutritional intervention).

Quest for disease mechanism. Clinical trials in food and nutrition have considerable potential significance for the biomedical sciences as far as disease mechanisms are concerned. They will enable us to test and identify food properties and compounds, the alteration of which may facilitate the prevention and management of disease.

Food and health relationships

Presumptive causality and its evaluation. One of the major tasks for clinical nutrition trials is to establish causality among the many established food and health relationships which have emerged from cross-sectional community-based studies, and from observational, cohort and case-control studies.

There remain areas of human biology likely to be significantly affected by diet for which the prima facie case for food component dependency, through identification of relationships, have scarcely been advanced. These would include the following: menstrual function,[26] menopause,[27] immune function,[28] cognitive function,[29–32] olfaction and memory.[33]

Assignment of importance. If causality is established by way of controlled interventions and/or trials, the relative importance of nutritional factors, as opposed to others, needs consideration as does the dose–response relationship and the durability of, and tolerance to or adaptation to, the effects. One of the remarkable features of the human diet appears to be the range of options compatible with health, presumably due, in part, to the alternative ways of achieving the same biological outcome (e.g. antioxidation through the selenium metallo-enzyme glutathione peroxidase or through tocopherols).[34,35]

Dealing with food chemical and dietary complexities. Because of dietary intricacies or complexities, it is important to consider whether clinical trials will miss the effects of a potential food factor or only see them in the context of other nutritional or non-nutritional problems (e.g. combined as opposed to single antioxidant deficiency, different levels of physical activity). It is an advantage to design trials so that several factors can be considered at once.[13,27,36,37]

Some clinical trials in nutrition will have to mathematically model food intake as meals, day-long patterns or patterns over longer periods. We know little, for example, about meal time bioavailabilities or responses to some nutrients;[38] of diurnal variations of nutrient intakes or their effects (e.g. thiamin at breakfast from cereals, zinc at the evening meal from meat);[39] or of the day-to-day fluctuations in nutrient intakes where the nutrient in question is stored for shorter or longer time periods. A good example of the ways in which changing nutrient intake may or may not be reflected in blood and tissue nutrient status comes from vitamin A physiology. Preformed vitamin A intake is markedly variable with post-prandial increases in retinyl esters dependent on chylomicron transport. However, with hepatic storage, since there is a serum homeostatic mechanism in retinol-binding protein (RBP),[40] fasting vitamin A concentrations are rela-

tively constant. In contrast, provitamin A carotenoids are transported by lipoproteins, along with non-provitamin A carotenoids such as lycopene.

There are also seasonal variations in dietary intake and those that take place in relation to intercurrent illness or treatments for these illnesses. More than is the case with single drug studies, food-derived nutrients or other components present demanding design requirements. At the very least, clinical trials in food and nutrition will always require documentations or standardization of the background diet. Ultimately, designers may wish to take into account the dynamics of human eating by undertaking] studies in non-steady state conditions. Rapid and repeated measurements and advanced data processing may allow this. For example, continuous measurement of energy expenditure may allow an understanding of its determinants in non-steady state conditions.

Nutritional contributors to metabolic pathways: The nutritional mechanisms for health and disease

Much of the focus of the study of food and metabolic pathways and, through them, health outcomes has been on intermediary metabolism, the role of vitamins, and the related focus on what we now regard as classical vitamin deficiency syndromes.[41] The relatively later appreciation of essential trace elements greatly expanded the knowledge of nutritionally dependent metabolic pathways, notably those dependent on the many metallo-enzymes.

Inborn errors of metabolism have greatly improved our understanding of nutritional influences on metabolism (e.g. phenylketonuria). The food factors, which were found to inhibit enzymes or induce them, further developed this area.

The realization that food and beverage intakes could be important in carcinogenesis paved the way for an analysis of diet–genetic interactions which could alter metabolic events.[42,43]

The most recent shift in thinking has been the recognition that food intake and nutritional status can modulate gene expression.[13,44] Each of these modes of operation of diet on metabolism may be addressed in a clinical nutrition trial. Understanding them will advance the understanding of the nutritional basis of health and disease. However, it must also be acknowledged that the nutritionally related ways in which health is achieved and diseases develop are more complex, involving socio-anthropological and behavioural pathways (e.g. social anchorage, food beliefs and behaviour knowledge).[45,46]

Advances in food technology

The development of nutrition science and food technologies has brought new insights to the knowledge of food for use in health and disease. This is most obvious in the conceptualization of functional foods; that is, food for specified health uses. Functional foods may be categorized into medical and non-medical. They are sometimes called designer foods, if they are newly created, although some are traditional foods or derived from traditional food technologies. It could be argued that the way in which breakfast cereals are being transmuted to deal with perceived micronutrient problems or dietary fibre deficiency problems make them 'functional'. Tofu or soy beancurd, if used as a source of phytoestrogens, may be an example of a traditional food requiring functional food categorization for this application.

The following three criteria may be used to define functional foods:

1. Foods which are positioned in the diet to contribute to the maintenance and improvement of health or to the management of disease. Given that functional foods are intended for regular, if not daily, consumption, their development has implications for the nature of food habits and food practices and therefore health outcomes.
2. Edible or potable items made from common food ingredients and used as foods, rather than in the common forms of medication, such as tablets or capsules; the grey area is that of liquids and powders with potential specific health uses.
3. Items that can be consumed by individuals in the course of usual eating episodes.

Another advance in nutritional science has been the development of 'nutritionally complete' (as far as we know) formula feeds, such as Modifast®, Ensure®, Sustagen®, and other diets which are 'elemental' (i.e. broken down to the basic building blocks of macronutrients; for example, amino acids or peptides instead of protein). Formula feeds are designed for use by individuals suffering from diseases which make the use of ordinary solid foods difficult or where ordinary food needs to be replaced for therapeutic reasons. The products can, however, be used as supplementary foods although they are formulated to sustain life in their own right.

Functional foods may be consumed by healthy people or individuals with borderline health. They aim either to prevent the deterioration of health or maintain health in those who have definable health problems. Formula feeds are used where disease prevents ordinary food from being used or where ordinary food must be avoided for extended periods of time; thus, a requirement of such products is that they are nutritionally complete. The foods may also be used to assist recovery from acute illness or surgery (e.g. by stimulating immune function or wound healing) and to prevent the development of complications (e.g. those of diabetes).

Mostly, functional foods will be consumed by healthy or borderline-healthy individuals with the aim of maintaining health or preventing the deterioration of health, respectively. Alternatively, formula feeds may be consumed by individuals suffering from certain diseases with the aim of assisting recovery and preventing the development of complications of disease.

Objectives and end-points for clinical trials in relation to the use of food, nutrients or other food components

Objectives

Exploring the nutritional basis of health and disease. *Socio-anthropological and behavioural objectives* One of the most crucial issues in food and health is what determines, and how change can be wrought in, food selection. To date, this enquiry is often left to market researchers but clinical trials in this area will become more important as certainty about attribution is required, along with the extent of unintended consequences. For example, researchers need to explore what the substitution of low for high sodium (or sweetness, or fat, or spiciness, or dietary fibre) food or cooking practices does to overall food selection, and why.

Food or meals with particular physiological effects A particular food or a meal can have physiological effects greater than the sum of their components or parts and these are worthy of study. For example, milk or yoghurt may yield various biologically active properties (angiotensin-converting enzyme inhibitors)[47] or hormone-like compounds (e.g. the caseomorphins) in a way that isolated protein may not.[48]

Breakfast has been much studied as a meal which can induce changes in cognitive or motor function.[49] More work is required on snacking and other occasions of eating, together with overall patterns.

Nutrient effects These may be located at the assimilation, lymphatic or blood transport, tissue, enzymic or molecular level, as discussed earlier. Each location could be the focus of a clinical trial.

Non-nutrient components of food As knowledge of the myriad components of food increases, along with knowledge of their biological effects on the human species, clinical trials aimed at discovering their effects on human biological mechanisms will be carried out. For example, trials could be conducted to determine whether phytoestrogens operate on a hierarchy of receptors in conjunction with endogenous oestrogens; whether they operate in bone in the same way in men and women; and whether they alter prostatic function.[26]

Enhancing health status. There are expectations that food will not only prevent us from dying of hunger, developing deficiency diseases and, when eaten correctly, allow us to avoid diseases of excess, but that it will somehow allow us to feel better on a day-by-day basis. Few would doubt that it does these things (as judged even by the assuagement of hunger), but the scientific basis for this is weak and precludes the development of food products which might further enhance health.

More specific end-points might therefore be helpful, such as sense of well-being, mood and sense of humour, which usually require scaling techniques or composite scores.[50–52] These techniques may be sensitive indicators of food toxicity as well as food benefit.[53]

Decreasing risk or preventing disease. This requires the definition of risk factors for each nutritionally related disease. Some of these diseases may as yet be obscure. The food hormone–human physiology paradigm is an example of how new possibilities for nutritional pathways to disease can be opened up for investigation. The steps in enquiry, then, are to trial food and food components which may alter risk factors, followed by the trialling of disease process, and then by the trialling of disease outcomes.

Controlling a disease or preventing its complications. Disease process (as in arterial wall changes, cognitive impairment or factors underlying these events), disease outcome (e.g. ischaemic heart disease or dementia) or disease complications (e.g. congestive heart failure or incontinence) are each amenable to clinical trials with a nutritional intervention but time-frames to development will affect cost and feasibility, as will sample size requirements. At the end of the day, it will sometimes be necessary to make the best fit of different lines of evidence.

Curing a disease. A cure is much more likely with a rapid-onset food component deficiency (e.g. iron deficiency diseases) or tissue accumulation (e.g. of fat in obesity or cholesterol in the arterial wall), unless there is irreparable damage, than with slow-onset nutritionally related NCD (e.g. osteoporosis).

Table 1. Some adverse effects and toxicological issues for clinical trials in nutrition

System	Potential adverse effect	Example of food factors
Cardiovascular system	Cardiac output	Alcohols as cardiac depressants
	Atherosclerosis	Various food factors which contribute to atherogenesis
Central nervous system	Behavioural	Biogenic amines, salicylates, MSG[56]
	Cognitive function	Zinc[18], gingko alkaloids, oxidants, (e.g. PUFA), antioxidants (e.g. glutathione)[93]
	Headache	Variable caffeine intake
	Visual	Oxidants, PUFA
Gastrointestinal tract	Nausea, vomiting, gut motility	Akinetic agents, food physico-chemistry, trypsin inhibitors
	Digestion, absorption	Probiotics/antibiotics, glutamine deficiency
	Gut microflora, gut immunity	
Genetic	Mutagenesis	Aflatoxins
	Oncogenesis	Food viruses
Growth	Linear growth velocity	Growth factors and antigrowth factors
Hematologic	Erythropoiesis, myelopoiesis, megakaryopoiesis	Various hematinic deficiencies
Immune system	Natural	Folate, glutamine deficiency
	Humoral	Protein deficiency
	Cellular	Various micronutrient deficiencies, glutathione deficiency[57], flavonoid deficiency[58]
Musculoskeletal system	Muscle mass and function	Protein deficiency, respiratory chain inhibitors
	Bone density	Osteoclast activators
	Joint architecture	Excessive nucleic acid intakes
Respiratory system	Bronchial reactivity	Salicylates, MSG, biogenic amines, and other sensitizers
	Diffusing çapacity	Moulds, aflatoxins

PUFA, polyunsaturated fatty acids; MSG, monosodium glutamate

Arrest of the disease process is more likely than is a cure. In both situations, factors which may lead to nutritional relapses need to be understood and, ideally, taken into account in longer term trials.[54]

Documenting and defining adverse effects. The question of appropriate toxicology is an important one in clinical trials of a nutritional kind (Table 1). In many ways, adverse effects should be sought as for drug trials. The reasons why assumptions should not be made about safety on the grounds that ingredients have long been in use are those of dose, vehicle of usage, duration and timing of exposure, food cultural guidance and constraints, and the health status of exposed individuals. Predicted total intakes, on the basis of prevailing food habits, become particularly important in relation to acceptable daily limits.[55]

Much contemporary food toxicology (or food additives toxicology) is restricted to questions of mutagenicity or adverse organ effects (e.g. liver, kidney, skin) in experimental animal studies. Questions of change in human intestinal microflora, cognitive function, cardiorespiratory performance, muscle function, immune function and the like are rarely addressed. Again, whatever the clinical trials show, long-term monitoring and surveillance needs to be possible and available in places where new products are introduced.

Considering the nutritional consequences of pharmacotherapeutic interventions. Inasmuch as pharmacotherapy may alter food intake, change body composition or condition essential nutrient requirements, nutritional end-points are a reasonable part of clinical trials in general.

End-points

Each objective presents a range of possible end-points for clinical trials, embracing the following categories of variables: food intake, body composition, functional status (e.g. strength and work performance, immune function, cognitive function), disease risk factors (e.g. diabetes, cardiovascular disease, osteoporosis) and disease incidence (e.g. cancer). Table 2 lists various end-points for clinical trials in nutrition.

Food and nutrition versus drug trials

Similarities and dissimilarities There are similarities and dissimilarities between food or nutrition and drug trials. Both food and drug trials may provide evidence of ways in which health may be improved and maintained. They may also address similar morbidity and mortality. However, there are several dissimilarities between food or nutrition and drug trials which are listed in Table 3. Good study design and narrow entry criteria for subjects being studied, with rigorous conduct of the study, will help to reduce the caveats in food and nutrition trials. Particular note should be taken of the following: (i) the fact that food is generally recognized as safe, although this will change (e.g. progress towards phase 1, 2 and 3 trials); (ii) the need to evaluate the side-effects and toxicology of newer foods and food technologies; (iii) the trend with drug trials that, while a single outcome is usually of interest, this is changing towards quality of life measures and total morbidity and mortality: these measures can be an invaluable part of nutrition trials; (iv) the likely higher adherence with drugs and, therefore, the extra insight, effort and design required with food studies; (v) bias in application of findings through advocacy by food or pharmaceutical industries; and (vi) the expectation that food intervention will be safer than drugs, although novel food products may be quite uncharacteristic of the historic food supply and, therefore, of relatively unknown risk.

Risk–benefit considerations Given the above analysis, risk–benefit considerations may be more subtle and longer term with food than with drugs but no less in need of evaluation.

Methodological issues

A clinical trial is an epidemiological study design. It differs from cohort and observational studies. A clinical trial allows the investigator to allocate treatment at random and has the potential to produce high quality results that resemble the controlled experiment.[59] Clinical trials can be categorized as being therapeutic or preventive. Nutrition support is a special form of therapeutic trial, while community nutrition intervention is a trial aimed at disease prevention (primary prevention). Nutrition support almost always focuses on individuals. Primary prevention trials in nutrition, on the other hand, assess end-points at the individual and population levels.

Nutrition support and community nutrition intervention trials, while each having a different focus in their objectives, require similar consideration in the design and conduct of the trial, sample size calculation, data base management, and statistical analysis. Clinical trials in nutrition require special consideration. Such consideration includes that of methodological issues related to the maintenance and assessment of background diet, and measurement of errors associated with nutrition assessment (not necessarily contemplated when they are not laboratory-based, as with anthropometry).

Design and conduct of clinical trials

There are at least three issues in the design and conduct of clinical trials: (i) identification and recruitment of a study population; (ii) delivery of the intervention and assessment of compliance; and (iii) ascertainment of quality end-points.[60]

Identification and recruitment of a study population. Clinical trials begin with design issues in population selection. Within the population hierarchy, a study population is nested under the reference population to whom results of the intervention trial are generalizable. Members of the reference population who meet the entry criteria of a trial are called the experimental population. In a nutrition trial, an experimental population eliminates individuals who can potentially bias intervention outcomes or contribute to a decreased power of the statistical test. At the same time, this may limit the ultimate generalizability of the findings. A long-term clinical trial relies on complete and accurate follow-up information. Thus, an experimental population selection needs to take into account follow-up rate. Once the experimental population is defined, members can then be invited to take part in the study. A study population consists of individuals who are eligible and willing to participate in the trial. In a nutrition trial, members of the study population would be allocated to either a dietary intervention group(s) or comparison group(s).

The ultimate goal of a nutrition trial is to establish the effect of the intervention. For the trial outcome to be sufficiently explained by the intervention, factors which determine the experimental population, the characteristics of the study population and, finally, the intervention allocation also

Table 2. End-points for clinical trials in nutrition

Intervention	End-points		Significance and cautions
	Category	Variable	
Socio-anthropological and food beliefs: social network, economic factors, organizational factors, food supply Nutritional education or behaviour therapy Food commodity comparisons (e.g. meat versus fish, rice versus wheat)	Food intake	Food practices Food indices (food variety, nutrient-dense food, energy-dense food, food acculturation scores) Alcohol intake Nutrient indices Other food component indices	When changed in favorable direction, improvement in well-being, and/or health status may follow, as judged from other studies Evaluate consequential change in background diet, food cultural intactness (eg Swedish study of social factors on nutrient intakes from dairy products)
Food/nutrient supplementation or restriction Food commodity comparisons Food analogue (e.g. functional food or formula feeds) Physical activity Pharmacological agent	Body composition	Fat free mass Fat mass Fat distribution Bone density Water Organ size	Indicative of protein and related whole body nutritional status Reflects energy stores and metabolic phenomena of importance in chronic non-communicable diseases Bone strength, fracture proneness, nutrient stores (e.g. zinc) Integrity of body water regulatory phenomenon Relates to specific organ function (e.g. cardiac, immune system (spleen)) Consider extent to which weight change comprises a body compartment and its function. Assessment of nutritional reserve and margin for error in tissue stores
Food/nutrient supplementation or restriction Food commodity comparisons Food analogue (e.g. functional food or formula feeds) Physical activity Pharmacological agent	Functional status	Muscle strength Work performance Haematological status Vision (e.g. dark adaptation) Cognitive function Immune function	Indices of performance, well-being, and proneness to disease addressed. Function may fluctuate and not be related to intervention; thus, study design needs to be of sufficient duration to take this into account Degree of unintended functional compromise in one domain when another is advantaged must be considered
Food/nutrient supplementation or restriction Food commodity comparisons Food analogue (e.g. functional food or formula feeds) Physical activity Pharmacological agent	Risk factors for disease	*Cardiovascular*: abdominal fatness, blood pressure, lipoproteins, platelet function, glycaemic status, physical fitness *Diabetes*: abdominal fatness, physical inactivity *Osteoporosis*: body mass index, calcium intake, sodium intake, caffeine intake, phytoestrogen intake, physical activity, cigarette smoking *Neoplastic disease*: body fatness, fat intake, plant food intake, preserved food intake, alcohol intake, physical activity, cigarette smoking	Greater opportunities for prevention of disease once risk defined and corrected Correction of risk factor may have other effects which are adverse
Food/nutrient supplementation or restriction Food commodity comparisons Food analogue (e.g. functional food or formula feeds) Physical activity Pharmacological agent	Mortality	Disease-specific mortality Total mortality	Encourage disease avoidance through nutritional and other means and strategies which will have favourable effects on different kinds of premature death It may be difficult or costly in time to detect or prevent chronic disease-related mortality